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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/673,538	09/29/2003	Shimin Liu	N12-001	1846

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EXAMINER	
WALLENHORST, MAUREEN	

ART UNIT	PAPER NUMBER
1743	

DATE MAILED: 12/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/673,538	LIU ET AL.	
	Examiner	Art Unit	
	Maureen M. Wallenhorst	1743	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 6 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 22-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 22-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/29/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. Claims 12, 32-33 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

On line 5 of claim 12, the phrase "the treated specimen" lacks antecedent basis and should be changed to –the exposed specimen--.

On the last line of claim 32, the phrase "the disease" lacks antecedent basis since the preamble of the claim recites a method of determining whether a subject is at risk of developing or suffers from cerebral vascular trauma. Therefore, on the last line of claim 32, the phrase "likelihood that the subject may develop or has developed the disease" should be changed to –likelihood that the subject may develop or has developed cerebral vascular trauma or bleeding--.

On the last line of claim 33, the phrase "the presence of erythrocytes" should be changed to –the presence or past existence of erythrocytes in the sample or specimen—so as to be consistent with the preamble of the claim, which recites a method of detecting the presence or past existence of erythrocytes in a specimen or sample.

On line 7 of claim 35, the phrase "9-BBN" is indefinite since it is not clear what this abbreviation stands for. On lines 7-8 of claim 35, the phrase "The Grignard Reagent" is indefinite since it is not clear what chemical this reagent refers to.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 6-7, 12, 14, 20-28, 31 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Schwartz (US Patent no. 4,378,971).

Schwartz teaches of a method and apparatus for quantitatively determining the level of hemoglobin in a biological sample. The method is used for diagnosing diseases in an individual such as intestinal tumors (see lines 24-26 in column 1 of Schwartz), and is used as an occult blood assay (see lines 57-59 in column 1 of Schwartz). The method comprises the steps of collecting a biological sample such as feces or urine, and combining the sample with a reacting solution specific for heme compounds such as hemoglobin. Schwartz teaches that if the sample is a feces sample, the sample should be homogenized in a saline solution. See lines 50-51 in column 8 of Schwartz. The reacting solution contains a strong reducing agent or salt. Schwartz teaches that the strong reducing agent is preferably ferrous oxalate or ferrous sulfate, but also indicates that other reducing agents may be used. See lines 37-48 in column 5 of Schwartz. The reducing agent causes the heme portion of hemoglobin to be converted to porphyrin. During the conversion reaction, iron is removed from the non-fluorescing heme-containing porphyrin, resulting in the iron-free fluorescing protoporphyrin, which fluoresces red upon exposure to

ultraviolet light at a wavelenth of approximately 408 nm. Therefore, the removal of the iron from the porphyrin molecule in heme forms a porphyrin-like fluorescing compound, i.e. protoporphyrin. See lines 25-58 in column 6 of Schwartz. The fluorescence of the sample is then measured with a fluorimeter or spectrofluorophotometer, and the fluorescing porphyrins are found to show fluorescence peaks between 500-630 nm. See lines 41-43 in column 7 and lines 3-21 in column 8 of Schwartz. Schwartz teaches that the fluorescence not related to the heme compound reaction in a biological sample must be removed from the sample in order to obtain an accurate measurement of the amount of hemoglobin or blood in a sample. See lines 55-68 in column 2 and lines 1-8 in column 3 of Schwartz. The measured fluorescence is compared with standard known levels of hemoglobin or protoporphyrin concentrations, and the concentration of the heme compounds or hemoglobin in the biological sample is calculated. Schwartz also teaches of a kit to be used in performing the method. The kit comprises a structure 18 having a plurality of reaction chambers 19a, 19b, 20a and 20b therein. These reaction chambers are provided with a cap 21 and a transparent window 22 that enables fluorescence of the material in the chambers to be assayed. Some of the chambers contain a reaction solution comprising a reducing agent. Biological test samples are then added to each of the chambers, where any heme compounds in the samples are reduced to a fluorescent protoporphyrin compound. Other of the chambers contain a non-reducing solution to serve as blank chambers that measure only naturally occurring fluorescence in a test sample. It is inherent in the kits taught by Schwartz that they contain instructions and protocols to be used with the components of the kit in order to perform a certain method, i.e. a method of determining blood products in a biological sample. See lines 61-68 in column 9 and lines 1-63 in column 10 of Schwartz.

5. Claims 9-11, 29-30 and 33 are rejected under 35 U.S.C. 102(a) as being anticipated by Liu et al (abstract from Society for Neuroscience Abstracts submitted in the Information Disclosure Statement filed on September 29, 2005).

Liu et al teach of a method for detecting red blood cells or erythrocytes in a cerebral specimen. The method comprises the step of treating a cerebral tissue sample with a solution of 0.2% sodium borohydride, a strong reducing agent. Liu et al teach that the sodium borohydride causes the erythrocytes in the sample to produce an intense autofluorescence while background fluorescence is greatly reduced. The fluorescent images of the erythrocytes are obtained with a fluorescent spectrometer or fluorescent microscope. It would be inherent that the erythrocytes tested in the method of Liu et al would fluoresce with a spectrum from about 530-670 nm as in the instant invention since the same strong reducing agent as used in the instant invention is applied to the same type of specimen, i.e. blood cells. The method taught by Liu et al serves to determine the extent and spatial distribution of erythrocytes trapped in cerebral tissue microvasculature.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. Claims 5, 9-11, 13 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz (US Patent no. 4,378,971). For a teaching of Schwartz, see previous paragraphs in this Office action. Schwartz fails to teach that the reacting solution contains saline therein, fails to teach that the method can be used to detect erythrocytes in a sample, and fails to teach of purifying a fecal sample before reacting the sample with the reducing agent.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to include saline in the solution of reducing agents taught by Schwartz since saline is disclosed by Schwartz as being used for homogenizing a fecal sample, and the inclusion of saline in the solution of reducing agents would avoid having to separately homogenize a fecal sample, and would allow a single solution to facilitate both the homogenization of a fecal sample and the reduction of the porphyrin molecules therein. It also would have been obvious to one of ordinary skill in the art to realize that the method taught by Schwartz can be used to detect erythrocytes in a biological sample since Schwartz teaches that the method is used to determine hemoglobin and heme compounds in a sample, and erythrocytes are well known as containing hemoglobin therein. Therefore, when hemoglobin is detected using the fluorescence method taught by Schwartz, erythrocytes in the sample are also inherently detected since hemoglobin originates from erythrocytes. It also would have been obvious to one of ordinary skill in the art to purify fecal samples collected in the method taught by Schwartz in order to remove materials that might interfere with the production of an accurate fluorescence measurement since Schwartz teaches that fecal samples contain substances therein that produce fluorescence that is not related to the

heme compound. By purifying the fecal samples, these compounds would be removed to obtain a value for fluorescence that is due specifically only to the porphyrin-like compounds formed from heme.

9. Claims 1-8, 12-13, 26-28, 32 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. (abstract from Society for Neuroscience Abstracts submitted in the Information Disclosure Statement filed on September 29, 2005). For a teaching of Liu et al, see previous paragraphs in this Office action.

Liu et al fail to teach that the fluorescent method for detecting red blood cells in cerebral microvasculature can be used for detecting occult blood in a specimen such as feces and for determining whether a subject is at risk for developing a disease associated with occult blood or with cerebral vascular bleeding. However, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to use the method taught by Liu et al for such a purpose since the detection of occult blood in a sample such as feces and the detection of a disease associated with occult blood depends on the detection of red blood cells in a specimen, and Liu et al teach that red blood cells in a biological specimen such as cerebral tissue can be easily detected by treating the specimen with a strong reducing agent (i.e. sodium borohydride) and observing any resulting fluorescence since red blood cells when present, react with the reducing agent to produce a strong fluorescence.

10. Claims 14-19, 22-25, 31 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al in view of Schwartz. For a teaching of Liu et al and Schwartz, see previous paragraphs in this Office action. Liu et al fail to teach of incorporating the reagents and materials necessary for detecting red blood cells in a biological specimen into a kit form.

Based upon the combination of Liu et al and Schwartz, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the reagents and materials taught by Liu et al as necessary for detecting red blood cells in a biological specimen into a kit form since Schwartz et al disclose that it is advantageous to incorporate all of the necessary reagents and materials for detecting blood in a sample into a kit form containing separate containers for the reagents and instructions so as to have all of the required materials for performing the method in one convenient place in the proper amounts and concentrations so that the method may be performed efficiently and quickly.

11. Applicant's arguments filed September 29, 2005 have been fully considered but they are not persuasive.

The previous objection to the abstract made in the last Office action mailed on March 29, 2005 is withdrawn in view of Applicants' amendments to the abstract. The previous rejections of the claims under 35 USC 112, second paragraph made in the last Office action are also withdrawn in view of the amendments made to the claims. However, because of Applicants' amendments to the claims, certain of the amended claims are rejected under this statute as set forth above.

Applicants argue the rejection of the claims under 35 USC 102 and 35 USC 103 as being anticipated by or obvious in view of Schwartz by stating that the chemistry used by Schwartz to detect blood in a sample is an acid chemistry rather than a single strong reducing agent. Applicants argue that Schwartz uses a combination of a reducing acid, a reducing salt and heat to detect hemoglobin, and that the ferrous oxalate or ferrous sulfate used by Schwartz et al is only a weak reducing agent. Applicants argue that the fluorescent species that results in the method of

Schwartz is different than the fluorescent species resulting from the instant invention since the resulting species have different emissions at different excitation wavelengths. Finally, Applicants argue that the times and temperatures required for the chemical reaction differ between the instant invention and the method taught by Schwartz.

In response to these arguments by Applicants concerning the reference to Schwartz, it is first noted that Applicants are arguing the different chemistry used between the instant invention and the method taught by Schwartz, however, the claims as presently written, do not distinguish this different chemistry for the following reasons. First, the instant claims do not limit the reacting solution to only contain a single strong reducing agent since the open language of "comprising" is used. Therefore, the claims do not preclude the addition of other components such as a reducing acid or the application of heat to the method. The claims do not limit the strong reducing agent to a single chemical. Therefore, the combination of the oxalic acid and either the ferrous sulfate or ferrous oxalate taught by Schwartz can constitute a "strong reducing agent" since both oxalic acid and either ferrous sulfate or ferrous oxalate are reducing agents in and of themselves, and together, they would cumulatively produce a stronger reducing environment. Secondly, the strong reducing agent as recited in the claims is not defined in the specification by its reduction potential. Therefore, the strong reducing agent as recited in the instant claims is not limited to only chemicals with specific reduction potentials. Third, the different fluorescent products produced in the method of the instant invention having a specific fluorescence emission is not being claimed, rather, the method steps for detecting blood in a sample is being claimed. In addition, the independent claims do not recite the fluorescence excitation used or the fluorescence emission of the product produced as a result of the reaction

between blood cells and the reducing agent. Therefore, this argument is moot with respect to all of the claims except dependent claim 8. Finally, the fact that the method of Schwartz involves different times and temperatures required for the chemical reaction to occur is also moot since the time and temperature at which the method of the instant invention occurs is not presently recited in the claims.

Applicants' arguments concerning the reference to Kerwin et al are persuasive, and therefore, the previous rejection of the claims under 35 USC 103 as being obvious over Schwartz in view of Kerwin et al is withdrawn.

This Office action contains new rejections under 35 USC 102(a) and 35 USC 103 based upon the reference to Liu et al (abstract from Society for Neuroscience Abstracts submitted in the Information Disclosure Statement filed on September 29, 2005). This Office action is being made final since where information is submitted in an IDS after the first Office action with a fee, the examiner may use the information submitted and make the next Office action final whether or not the claims have been amended, provided that no other new ground of rejection which was not necessitated by amendment to the claims is introduced by the examiner. See MPEP 706.07(a).

The reference to Liu et al (from the Journal of Cerebral Blood Flow and Metabolism) submitted in the IDS filed September 29, 2005 is crossed out since this same reference was already considered and made of record on the PTO-892 form attached to the last Office action.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maureen M. Wallenhorst whose telephone number is 571-272-1266. The examiner can normally be reached on Monday-Wednesday from 6:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden, can be reached on 571-272-1267. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maureen M. Wallenhorst
Primary Examiner
Art Unit 1743

mmw

November 29, 2005

Maureen M. Wallenhorst
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